

REMARKS

Claims 1-11 were present in the application as originally filed and are currently pending in the application.

Rejection Under 35 U.S.C. §103(a)

Claims 1-11 were rejected under U.S.C. §103(a) as allegedly being unpatentable over Elger in view of Schwartz et al (U.S. Patent No. 5,523,292).

According to the Office Action, it would have been obvious to one of skill in the art at the time the claimed invention was made to treat stroke with ancrod as allegedly disclosed by Elger by selecting for the time intervals and effective amounts which were shown to be effective in reducing restenosis as taught by Schwartz. Applicants disagree.

The use of defibrinogenation agents, such as ancrod for the treatment of stroke is not new. The novelty of the present invention lies in the administration of ancrod to achieve a specific defibrinogenation pattern associated with improved safety and efficacy. For example, this specific defibrinogenation pattern reduces the effect of adverse side effects such as intracranial hemorrhage (ICH).

To date, conventional stroke treatment with ancrod includes an initial defibrinogenation accompanied by subsequent administration of additional doses of ancrod to maintain hypofibrinogenation for five days of treatment (paragraph [0028] of specification). In comparison, the present invention, as claimed, calls for the administration of a single relatively rapid dose of ancrod to achieve “rapid initial defibrinogenation,” defined in the specification at paragraph [0020] as the rate of defibrinogenation, i.e., an hourly decrease in fibrinogen, in excess of 20mg/dL/hr, more preferably in excess of 25mg/dL/hr and most preferably in excess of 30mg/dL/hr. Subsequently, fibrinogen levels are allowed to normalize, that is, come back to basal levels *without* further administration of the defibrinogenation agent. Cessation of administration of the defibrinogenation agent followed by normalization of fibrinogen to pretreatment levels after a single initial dose is a critical feature of the claimed method.

Elger et al. does not, as the Office Action alleges, teach a method for treating stroke in a patient. Elger et al. reports the results of an evaluation of whether or not treatment with the fibrinogen-lowering agent ancrod exerts beneficial effects on experimentally induced brain lesions in two different rat models of focal cerebral ischemia. Lesions were induced by either occlusion of the left proximal middle cerebral artery (MCA) or by photochemically induced thrombotic infarction. Subsequently, lesion volume was evaluated using MRI.

The use of animal models, while they provide valuable insight into the physiology of human disease, in rare instances approximate the human disease sufficiently to draw any conclusions with respect to treatment outcome. For example, while spontaneous cerebrovascular diseases, including arteriosclerosis, are known to occur in various species of animals phylogenetically below humans, ischemic cerebral insults, are rare events in non-humans. Results from an animal model for a stroke are not predictive of a successful outcome in human stroke patients because results derived from animal models can be significantly affected by the under which the models are created and conditions of testing.

In support of this proposition, Applicants submit two references: 1) Molinari et al., Stroke vol. 7 no. 1 pp. 14-17 1976 and 2) Fukuda et al. (ILAR Journal, vol. 44 no. 2, pp. 96-104.) copies of which are enclosed for the Examiner's convenience. Molinari stands for the proposition that species used in experimental models of disease, although they may bear some anatomical and physiologic resemblance to humans, there are nonetheless significant anatomical and physiological differences that need to be considered when evaluating comparative neuropathology of cerebrovascular disease.

Like Molinari, Fukuda et al. characterize ischemic stroke as a uniquely human disease and discuss the limitations associated with the use of animals particularly rodents that are phylogenetically distant from humans. The skilled artisan, therefore, would not have an expectation of success of treating stroke in humans based on the teachings of Elger et al.

Schwartz et al. is cited for teaching doses of ancrod and dosage intervals effective in reducing restenosis. Schwartz et al. teach a method of reducing restenosis following post-cutaneous transluminal coronary angioplasty to remove atheromatous lesions, wherein the method involves administration of an effective amount of ancrod. Like Elger, the study is based on the use of ancrod in a porcine model of cardiovascular restenosis which seeks to prevent thrombus formation as a mechanism for reducing lesions resulting from restenosis. According to Schwartz et al., the particular dosage regimen and schedule of ancrod administration is dependent on the aim of therapy, in the case of restenosis to reduce or prevent thrombus formation. Schwartz et al. stresses, however, that ancrod must be administered relatively slowly in order to prevent excessive coagulation (col. 2, lines 49-51). Furthermore, Schwartz et al. suggests that maintenance doses may be administered at the end of the initial infusion period. According to Schwartz, administration of ancrod may be extended 1 to 2 weeks or longer (col. 3, lines 8-12.) Results regarding the efficacy of ancrod were based on the observation of restenotic lesions during necropsy.

As a preliminary matter, stroke, that is cerebral ischemia, is not the same as restenosis of coronary arteries, as taught by Schwartz et al. Stroke involves an interruption of blood flow in the vasculature of the brain either as the result of thrombus or hemorrhage whereas restenosis is a recurrent constriction or narrowing of the blood vessel. Additionally, like Elger, the experiments in Schwartz were conducted in a non-human animal model with the only metric of success being histological evaluation of restenotic lesions.

The Examiner argues that it would have been obvious to one of skill in the art to treat human stroke patients with ancrod as disclosed by Elger et al. using time intervals, and effective amounts that have been proven efficient in preventing restenosis. The Examiner states that restenosis is related to the onset of stroke in a patient. In fact, although both stroke and restenosis are associated with the cardiovascular system, the disorders are not the same, and it would not be obvious that a treatment that is successful for restenosis would be effective for the treatment of stroke.

While the use of a rodent ischemia model yields valuable, clinically relevant insights into the pathophysiology of ischemic stroke, it is not predictive of outcome in humans who have suffered ischemic stroke. Thus, it would not have been obvious to one of skill in the art to use ancrod to treat human stroke patients based on the teachings of Elger and Schwartz. At best, it might be "obvious to try," but that is not the appropriate standard. Under O'Farrell (853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988), the tripartite test used is to determine 1) whether the cited references show an enabling methodology, 2) suggest how to modify the prior art to obtain the applicant's success, and 3) provide reasonable evidence that the invention would be successful." Here, it is apparent that the references do not fulfill these criteria; there is no expectation, based on the teachings of the cited references, that administration of a defibrinogenation agent such as ancrod to achieve rapid initial defibrinogenation as claimed by Applicants would produce a positive outcome in a human subject.

Reconsideration and allowance of this application are respectfully requested in view of the remarks above. It is believed that the application is in condition for allowance, and such action is respectfully requested. If a telephone conference would be of assistance in advancing the prosecution of the subject application, the Examiner is invited to contact applicant's undersigned attorney at the number provided below.

Respectfully submitted,



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